# In *Silico*-derived Bedside Formula for Individualized Micafungin Dosing for Obese Patients in the Age of Deterministic Chaos

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There are 2.1 billion people worldwide who are overweight or obese. However, most current doses of drugs were derived for normal weight patients. For several drugs, the relationship between clearance and patient weight follows fractal geometry rules. Clearance directly determines the area under the concentration time curve (AUC) after i.v. infusion. For micafungin, AUC-to-minimum inhibitory concentration (AUC/MIC) ratios have a close deterministic relationship with efficacy in candidiasis; an AUC/MIC $\geq$3,000 is associated with 98% efficacy. We performed computer-aided clinical trial simulations of 100,000 patients with candidiasis to identify the lowest micafungin dose able to achieve AUC/MIC $\geq$3,000 in patients weighing up to 200 kg. We used the cumulative fraction of response to derive the formula "Dose (mg) = patient weight + 42" for use by the clinician at the bedside to individualize micafungin doses for overweight and obese patients. This paradigm for dose individualization could be used to optimize efficacy for many classes of anti-infective agents in obese patients.

Worldwide, the proportion of all adults who are overweight is now about 38%.[1] In 2013, 68% of Americans were estimated to be overweight or obese, whereas 32–34% were obese.[1] Overweight and obese are clinical terms used to identify body mass index value ranges, calculated by dividing weight in kilograms (kg) by the square of the height in meters. Greater than or equal to 25 kg/m$^2$ defines overweight, whereas $\geq$30 kg/m$^2$ defines obesity. In places such as South Africa, obesity rates are estimated at ~42% in women, whereas those in several Middle Eastern countries such as Qatar and Kuwait range from 44% in men to 60% in women.[1] In Tonga and Samoa, ~84% of men are either overweight or obese as are ~90% for women.[1] These global rates point to a new and unfortunate norm: the "average" patient is likely to be overweight or obese. Obesity predisposes to the metabolic syndrome, cancer, musculoskeletal disorders, depression, and increased hospitalization.[2] However, doses of many small molecules and biologics were optimized using patients who can be considered normal weight by current norms. This is a problem because patient weight affects drug pharmacokinetics and, hence, drug concentrations. This means that the obesity predisposes patients to increased hospitalization while simultaneously affecting the pharmacokinetics of many drugs used in the hospital.

The principle of alteration of pharmacokinetics has been formally tested in clinical experiments of antifungal agents, especially the echinocandins.[3,4] Echinocandins are first-line therapy for fungal infections, which are common hospital-acquired infections in patients with metabolic syndrome and cancer.[5] Dosing of echinocandins, such as micafungin or any other anti-infective agent for that matter, in overweight and obese patients who constitute a large portion of patients has hitherto been unexplored.[6,7] Echinocandins have a success rate of ~75% for treatment of candidiasis in the best of circumstances[5]; higher doses for both overweight and obese patients could improve efficacy.

Micafungin is used often for the treatment of candidemia and aspergillosis, based on a unique mechanism of effect that targets the fungal cell wall. For the treatment of candidiasis, doses of 100 mg a day are administered daily for 14 days after culture conversion, whereas 50 mg has been used for prophylaxis. Micafungin is generally well tolerated, but the serious adverse events include intravascular hemolysis, hypersensitivity and anaphylactic reactions, and hepatotoxicity. Because micafungin clearance is higher in obese patients compared to leaner patients, and because micafungin efficacy is closely linked to the ratio of the 0–24 hour area under the concentration time curve (AUC$_{0-24}$) to minimum

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**Table 1 Pharmacokinetic parameters in patients treated with micafungin**

|  | Pharmacokinetic parameter estimates used in subroutine PRIOR | Pharmacokinetic parameter estimates in 95,000 simulated subjects |
|---|---|---|
| $CL_D$ in L*hr$^{-1}$ (SD) | 26.50 ± 3.10 | 26.52 ± 3.10 |
| $V_c$ in L (SD) | 11.70 ± 2.98 | 11.76 ± 2.97 |
| $V_p$ in L (SD) | 18.30 ± 6.39 | 18.32 ± 6.41 |

$CL_D$, intercompartmental clearance; $V_c$, volume of central compartment; $V_p$, volume of peripheral compartment.

inhibitory concentration (MIC; $AUC_{0-24}$/MIC), heavier patients are predicted to attain lower micafungin efficacy rates than their leaner counterparts.[3,6,8–10] In patients with candidiasis, the micafungin exposures associated with optimal clinical and microbiological outcomes are serum $AUC_{0-24}$/MIC $\geq 3{,}000$; at this exposure, success rates are up to 98%.[6] When one accounts for protein binding difference (unbound fraction = $0.004 \pm 0.001$), these exposures are virtually the same as those derived in murine studies of candidemia.[9–15] Thus, the tight link between $AUC_{0-24}$/MIC and efficacy is deterministic. In a deterministic system, a particular input is always associated with a particular response (in this case, AUC/MIC ratio as input and efficacy as response), in this case, across different biological systems. On the other hand, obesity, by definition, leads to changes in body size and proportions, which affects rates of metabolism, including xenobiotic metabolism pathways, with the relationships best described by fractal geometry.[3,4,8,16–21] Fractal geometry itself is a branch of chaos theory, and describes well the relationship between micafungin clearance and patient weight.[3,19–23] For overweight and obese patients, we have demonstrated that micafungin clearance point estimate at each weight can be calculated from the formula:

$$\text{Clearance (L/hr)} = 1.04 * (M/66.3)^{3/4} \qquad (1)$$

where M is the patient's mass in kilograms, starting at 66.3 kg.[3,8] However, there is further variability around the point estimate, given that the human pharmacokinetic system is nondeterministic. As a result, a single input, such as a micafungin dose of 100 mg, can produce a wide distribution of drug exposures, such as $AUC_{0-24}$. Similar fractal relationships and variability hold for other echinocandins in the clinic (although with different fractal dimensions or power exponents), as they do for other anti-infective small molecules and biologics, so that these agents too may need dose optimization in overweight and obese patients.[4,18,24] Here, we took advantage of these relationships to derive individualized dosing tools for overweight and obese patients at the bedside, so that doses can be increased to match increases in clearance as weight increases. Indeed, micafungin's good safety at high doses makes this exercise possible.[25,26] We utilize Monte Carlo experiments, which were specifically designed by Metropolis & Ulam[27,28] for similar stochastic outputs and first benchmarked with fissile material. We utilized these simulations,

taking into account MIC variability of 5,346 clinical *Candida spp.* isolates from around the world,[29] to derive optimal micafungin dose rules for bedside use. Such pharmacometric-based simulations have been used extensively for dose derivation of anti-infective agents, are known to be accurate, and have been used for licensing studies with the Food and Drug Administration.[30–36] With this approach, we extend therapy individualization beyond choice of therapeutic agent to individualized dosing.

## RESULTS

First, we performed a PubMed literature search using the keywords "micafungin AND obesity" or "micafungin AND overweight." The search identified our pharmacokinetic work[3,8,37] as well as a single case report of one 203 kg patient successfully treated with the standard micafungin dose for candida urinary tract infection; micafungin concentrations were low in that patient.[38] Thus, in the absence of clinical data for either invasive candidiasis or candidemia, a modeling and simulation strategy was adopted.

We performed Monte Carlo simulations for 5,000 patients each to determine the expected $AUC_{0-24}$ distribution achieved after administration of i.v. micafungin doses of 100 mg plus 25 mg increment doses in patients with invasive candidiasis or candidemia. Simulations were performed at 66 and 68 kg, and then starting at 70 kg increased in 5 kg intervals until 150 kg, using pharmacokinetic parameter estimates and variability, shown in **Table 1**. In **Table 1**, we show that the simulations of 95,000 patients adequately recapitulated the original pharmacokinetic parameter estimates and variances used as prior data, which is internal validation that demonstrates that the simulation exercises achieved the pharmacometric distributions that were intended.

$AUC_{0-24}$ for each of the subject's clearances was identified for each of the doses, and target attainment calculated at each (MIC; i.e., at each $AUC_{0-24}$/MIC), given the MIC distribution. **Table 2** shows results of a novel external validation step, meant to determine if the simulations reflect real life exposures encountered in patients in the clinic. **Table 2** shows that our 5,000 simulated patients with a weight of 68 kg who were treated with 100 mg micafungin a day achieved the AUC/MIC ratio $>3{,}000$ (i.e., target exposure) in 70% of patients as compared to 77% observed in actual patients by Andes *et al.*[6] in clinical trials. The simulated percentage of patients is slightly lower because of the right skew of MICs in the Pfaller *et al.*[29] MIC data whose micafungin concentration range tested was $\geq 0.07$ mg/L as opposed to Andes *et al.*[6] whose minimum MIC was $\geq 0.04$ mg/L. Moreover, the simulated patients tested were all 68 kg vs. an average of 68 kg in actual clinical studies. **Table 2** also shows that the maximum and minimum AUCs and AUC/MIC in simulated patients, the range is higher in simulations but encompasses the clinical observation because ~10 times higher number of patients were examined in simulations compared with those in the clinical study, which mathematically leads to wider ranges and is to be expected.[39] Thus, **Table 2** shows that, overall, the simulation results are in good concordance with clinical observations.

**Table 2  Monte Carlo simulation derived exposures vs. those observed in patients**

| Patients or micafungin exposure | Simulation of 5,000 patients | Observed in 493 patients |
| --- | --- | --- |
| Minimum $AUC_{0-24}$ (mg*h/L) | 46.6 | 76.1 |
| Median $AUC_{0-24}$ (mg*h/L) | 95.5 | 94.1 |
| Maximum $AUC_{0-24}$ (mg*h/L) | 224.1 | 118 |
| Minimum $AUC_{0-24}$/MIC | 11.9 | 41.3 |
| Maximum $AUC_{0-24}$/MIC | 31,452 | 98,716 |
| Patients with $AUC_{0-24}$/MIC >3,000 | 3,690 (70%) | 277 (76.69%) |

AUC, area under the concentration time curve; MIC, minimum inhibitory concentration.

**Figure 1** demonstrates that the proportion of patients who achieved or exceeded the target exposure declined steeply with weight when the standard dose of 100 mg was used as a one size fits all for all weights, at all MICs. This is termed the cumulative fraction of response (CFR). **Figure 1** shows that by the 150 kg weight, the CFR had fallen by 20%, and was below 50% CFR. This means that the standard 100 mg dose would be suboptimal in heavier patients.

**Figure 2** shows the relationship between optimal dose and weight. Several possible rules between weight and optimal dose were explored, based on linear regression, shown in **Figure 2**. The equations derived, shown as rules 1 to 3 in **Table 3**, were further simplified by rounding off the slope and decimals to create rules 4 and 5. Next, each of these formulae were used to calculate the optimal doses at each of the patient weights, and used to calculate bias. Bias, which is the tendency of the rule to overstate or understate the true value, is shown in **Table 3**. Because a bias of zero is the best, as is a 95% confidence interval that crosses zero, **Table 3** shows that rules 1 and 4 had the least bias. The simpler of these two rules, for which one was derived from the other, was:

$$\text{Dose (mg)} = \text{patient weight} + 42 \qquad (2)$$

rounded to the nearest 25 mg, with rounding up starting at 12. This formula is proposed for use at bedside by clinicians.
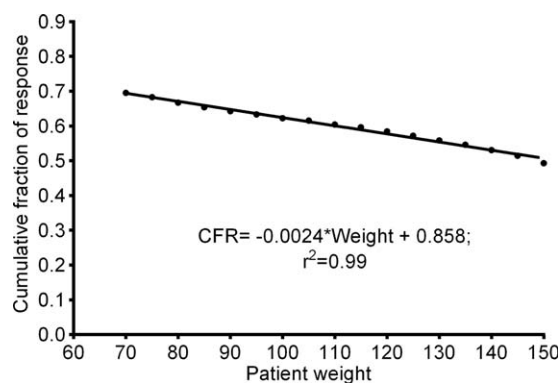


**Figure 1** Proportion of patients treated with 100 mg micafungin who achieve optimal micafungin exposures. The proportion of patients falls dramatically as weight rises, at a rate defined by the formula shown.

Next, this bedside formula was used to identify a dose for patients with weight of 200 kg, outside the rule derivation range. The formula calculates to a clinical dose of 250 mg. To cross-check this, we performed Monte Carlo simulations of a further 5,000 patients using clearances and variances at 200 kg, which revealed that this dose would or exceed the target exposure in 73% of patients. This CFR is very close to the 77% proportion in the Andes et al.[6] study that was associated with optimal efficacy. On the other hand, if such patients were dosed with the standard 100 mg of micafungin each day, the CFR was only 31%.

The more complex rule, shown in **Table 3** as rule number 1, has an even smaller bias than the simplified rule number 4 described above. This can be used for more accurate dose individualization by the pharmacometrician. However, in the case of the 200 kg patient for which we performed Monte Carlo simulations, this more complex rule gives the identical optimal dose of 250 mg derived using the simpler rule, so that based on parsimony, the simpler rule should be used.

## DISCUSSION

One of Paul Ehrlic's[40] well-known formulations is the concept of a "magic bullet," meaning selective targeting of a pathogen without affecting the patient (i.e., "selective toxicity"). In addition to pathogen selectivity, we must also aim with the precise dose of the therapeutic agent. An assegai achieves the maximal effect if the force used is well calibrated. Therefore, in addition to individualizing choice of a chemotherapeutic agent (the weapon), we hereby propose individualizing the dose of a chemotherapeutic agent (the force used). We took advantage of recent progress in population pharmacokinetics, fractal mathematics, and antimicrobial pharmacokinetics-pharmacodynamics to create a pathway for the identification of a simple formula that can be used at the bedside to individualize micafungin dosing and maximize microbial kill of Candida species. The modeling and simulation exercises we applied can be utilized for those other anti-infective agents used to treat many global health diseases whose clearance and even volume are affected by patient weight. Indeed, other echinocandins will also need to have similar work performed, given that agents such as caspofungin have even more complex fractal geometry relationships with weight.[4]

Second, we specifically offer a bedside formula for use by clinicians to treat candidiasis in overweight or obese patients, who are now well represented in hospitalized populations. Candida species cause common clinical problems in hospitalized patients all over the world. Although echinocandins are likely superior in terms of mortality and response compared to azoles, the efficacy rate is nevertheless still in the 70% range.[41] Efficacy is likely lower than the 70% in obese patients, given the lower AUCs. On the other hand, Andes et al.[6] have demonstrated that if AUC/MIC ≥3,000 was achieved, the patient success rate reached 98%. Thus, the proposed individualization of therapy could further boost micafungin efficacy up to 98%. Even though we propose doses of up to 250 mg, micafungin has a wide safety margin and thus kills Candida species at concentrations that do not harm patients (i.e., good selective toxicity). In one cohort of bone marrow transplant patients, up to 960 mg were administered every day for several

**Table 3  Different rules for calculating optimal micafungin dose**

|  | Formula | Bias (95% CI) | Coefficient of determination |
|---|---|---|---|
| Rule 1 | **1.03*weight + 41.93** | **−0.12 (−4.00 to 3.76)** | 0.92 |
| Rule 2 | 1.04*weight + 30.49 | 10.24 (6.36 to 14.11) | 0.99 |
| Rule 3 | Weight + 55.00 | −9.89 (−13.79 to −5.99) | 1.00 |
| Rule 4 | **Weight + 42** | **3.11 (−0.79 to 7.01)** | 0.92 |
| Rule 5 | Weight + 31 | 14.11 (10.21 to 18.01) | 0.92 |

CI, confidence interval.
The figures in boldface represent rules for which 95% CI for bias crossed zero.

weeks, with no worsening of adverse events, such as hepatotoxicity.[26] Thus, the doses of up to 250 mg that we propose are likely to be safe: after all the large doses are proposed because lower drug concentrations are achieved in the patients in the first place, and it is the concentration that is important in concentration-dependent toxicity and not the "dose size" per se. On the other hand, the relationship between weight and dose we derived was not tested for doses lower than 66.3 kg. Indeed, it is known that in the case of micafungin clearance in adult patients, there is no weight-related changes below this weight.[3,8] Thus, the algorithm we derived is only applicable to overweight and obese patients.

Third, we and others have proposed that intermittent dosing with micafungin is not only possible, but desirable.[9,37] Indeed, some clinical studies demonstrated better outcomes when higher peak concentrations of micafungin were achieved in patients with candidiasis.[37] In this case, the daily dose would be first calculated, and the dose multiplied by the dosing interval of the proposed intermittent dosing schedule. As an example, a once a week regimen (7 day dosing interval), would simply mean multiplying the daily dose (say 150 mg) by 7 for the once a week administration to give a dose of 1,050 mg. This latter strategy constitutes further refinement of aiming with the magic bullets, and brings us closer to another of Ehrlic's dreams for antimicrobial chemotherapy: "*Therapia magna sterilisans*," the "complete sterilization of a highly infected organism with a single dose."[40]

Fourth, the approach we utilized is applicable to the identification of optimized doses for patients who are overweight or obese for any drug whose efficacy is concentration-dependent and pharmacokinetics are influenced by weight. In addition, this can be applied to drugs with a narrow therapeutic index. If increased weight is associated with reduction in drug concentrations, then not only will efficacy decrease, but so will the probability of concentration-dependent toxicity. If the threshold concentration associated with increased probability of toxicity is identified, as is the case with aminoglycosides and calcineurin inhibitors, for example, then our simulation approach could also be used to identify the proportion of patients who would achieve or exceed the concentrations that increase the probability of toxicity. The dose that does not achieve that concentration associated with increased probability of toxicity, but is optimal for efficacy, is then chosen. Thus, an algorithm that calculates the optimal dose while minimizing the chances of concentration-related toxicity can be identified. The only assumption and requirement is that systemic clearance or volume of distribution of the drug increase as patient weight increases. Thus, our approach could be generalized to many pharmacophores.

A possible limitation to clinical recommendation is that our results are based on simulations, and not actual clinical trials. However, these types of computer-aided clinical trial simulations have been found to be highly accurate, and this pharmacometric approach has even been used for licensing drugs by regulatory bodies.[32–35] In addition, we added a second external validation step, which demonstrated that our simulations fit reasonably with actual clinical observations.

### METHODS
#### Target exposures
Micafungin exposures associated with optimal clinical and microbiological outcomes are serum $AUC_{0–24}/MIC \geq 3,000$.[6] This target exposure was used for all our simulations.

#### Monte Carlo simulations
We performed Monte Carlo simulations for 5,000 patients each to determine the expected $AUC_{0–24}$ distribution achieved after administration of i.v. micafungin doses of 100 mg and 25 mg increment doses in patients with invasive candidiasis or candidemia. Pharmacokinetic parameter estimates and variances shown in **Table 1** were entered in subroutine PRIOR of ADAPT 5, based on i.v. dosing with an infusion over one hour.[3,25,26] Although gender has an effect on clearance, the effect is small and clinically inconsequential, and was thus ignored.[3] The micafungin clearance point estimate at each weight was calculated from Eq. 1. The variability was based on variance encountered, which followed the same rule as clearance.
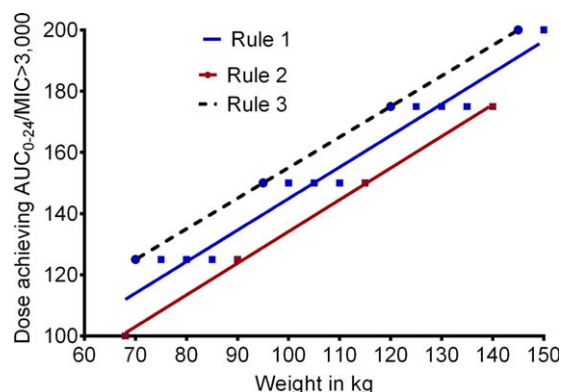


**Figure 2** Identification of different potential rules to be used at bedside to calculate micafungin dose. Three rules are shown; from rule 1 and 2 simplified rules were also created. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

A two compartment model was assumed, based on prior work.[3,8] At each of the weights, simulations were performed to generate a distribution of 5,000 clearances (100,000 candidemia subjects simulated in all). Next, 24-hour AUCs for each of the clearances was identified for each of the doses. Then, the $AUC_{0-24}$/MIC at each MIC was identified, and it was then determined if each achieved the optimal $AUC_{0-24}$/MIC ratio $\geq 3,000$. CFR was then calculated from the probability target attainment of $AUC_{0-24}$/MIC ratio $\geq 3,000$ for each MIC from $i$ (the lowest) to the highest ($n$) for a particular dose at a particular weight based on:

$$CFR = \sum_{i=1}^{n} PTA * F_i \qquad (3)$$

where $F$ is the proportion of Candida species at each MIC.

Several rules were then derived, based on simple linear regression of optimal doses vs. weight, the lowest 25 mg dose change vs. weight (because several 5 kg increment dose categories could have the same optimal dose rounded to the next 25 mg), and the highest 25 mg dose change vs. weight. In addition, we also simplified these rules by rounding of decimals to create potentially easier rules to remember. Next, bias of each of these rules was calculated. Bias (B), was calculated as:

$$B = \sum_{i=1}^{n} (T_i - P_i) / n \qquad (4)$$

where $T_i$ is the optimal dose identified using the Monte Carlo simulations, $P_i$ is the prediction from the rule, for a number of dose predictions $i$ of up to $n$. Bias was calculated with $P$ values for each of the patient weights from 70–150 kg based on the rule vs. Monte Carlo simulation-derived optimal doses.

In addition, we wanted to determine if the rule we derived for weight vs. dose would also apply outside the 70–150 kg weight range for which it was derived. After derivation of the rule, we performed the same simulations in patients with weight of 200 kg. This weight is encountered in about 0.2% of adults 20–29 years old (https://www.census.gov/compendia/statab/2012/tables/12s0210.pdf). We derived the optimal dose at that weight from the bedside rule we had derived, and then used that dose in Monte Carlo simulations to identify the CFR for the calculated dose.

### Hardware and software

All work was performed on a personal computer. Monte Carlo simulations were performed using ADAPT 5 software of D'Argenio *et al.*[42] Results were transferred to Excel spreadsheets and GraphPad Prism 5 software for further analysis and for better graphing. The rule for the relationship between optimal dose and weight was derived in GraphPad Prism.

## Study Highlights

### WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ More than 2.1 billion people alive today are either overweight or obese. Often, they clear antibiotics from their bodies more rapidly than normal weight patients, which may reduce the effective concentrations of these antibiotics. However, optimal doses for these patients have hitherto not been identified.

### WHAT QUESTION DID THIS STUDY ADDRESS?

✓ This study aimed to identify the optimal dose of the antifungal drug micafungin in overweight and obese patients being treated for invasive fungal infections.

### WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

✓ A simple formula that clinicians can use at the bedside to individualize micafungin doses in patients was identified. This is the first study to do this for obese patients.

### HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS

✓ This approach could be used to identify optimal doses for overweight and obese patients treated with other antibiotics.

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